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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,794	06/08/2001	Suzanne A. W. Fuqua	UTSK:348US/MBW	5270

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EXAMINER	
UNGAR, SUSAN NMN	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/877,794	FUQUA ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 22-25* is/are pending in the application.

4a) Of the above claim(s) *2 and 5* is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1, 3, 4, 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The Amendment filed May 12, 2004 in response to the Office Action of May 4, 2004 is acknowledged and has been entered. Previously pending claim 1 has been amended, new claims 22-25 have been added. Given the amendment of claim 1, response to the arguments presented in Applicant's Response to the Office Action dated October 14, 2003, received on February 23, 2004, is now appropriate. Claims 1, 3, 4, 22-25 are currently under prosecution and the Office response to the paper submitted February 23, 2004 follows.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejection are maintained:

Claim Rejections - 35 USC § 112

4. Claims 1, 3, 4 remain rejected under 35 USC 112, first paragraph, and new claims 22-25 are rejected under 35 USC 112, first paragraph for the reasons previously set forth in the paper mailed October 14, 2003, Section 7, pages 3-11.

Applicant argues that (a) the specification as written contains substantial information regarding the subject matter of the claims that is more than sufficient to enable one skilled in the art to make and use the claimed invention without undue experimentation wherein information regarding tamoxifen resistance is found on pages 2-3 and specification teaches that differential expression of TIE-2 is associated with tamoxifen resistant breast cancer and these findings provide the basis for methods directed toward diagnosis and prediction of tamoxifen-resistant breast cancer. The specification further teaches assay methods for TIE-2 polypeptide, methods of protein purification, methods of detecting variation in the expression of TIE-2, methods of making antibodies to TIE-2, and defines a TIE-2 protein on pages 8-10, which definition includes a high molecular weight TIE-2,

wherein a TIE-2 protein is defined in part by whether the protein in question has the ability to inhibit angiogenesis or to prevent metastasis or invasive tumor growth, (b) the specification exemplified the claimed invention using MCF-7 derived tumors which are assayed to demonstrate expression of TIE-2 and the results demonstrate that TIE-2 protein is upregulated in tamoxifen resistant MCF-7 cell line tumor as compared to tamoxifen-sensitive and estrogen stimulated MCF-7 cell line tumors. These results demonstrate that TIE-2 is a positive marker for tamoxifen-resistant breast cancer and may be used to differentiate between tamoxifen-resistant and tamoxifen-sensitive forms of breast cancer, (c) given the above, the specification is sufficient to enable one skilled in the art to make and use the claimed invention.

The arguments have been considered but have not been found persuasive because (a') the teaching of well known information regarding tamoxifen resistance and conventional methods of protein assay, methods of protein purification, methods of detecting variation in the expression of TIE-2, methods of making antibodies does not enable the claimed invention. In addition the broadly defined TIE-2 protein, that is a protein which includes proteins encoded by nucleic acid molecules substantially identical to a DNA sequence encoding a TIE-2, that is those with at least 50% identity to a sequence encoding TIE-2, proteins encoded by sequences that are capable of hybridizing to a nucleic acid segment containing the complement of a nucleic acid molecule encoding TIE-2 under a broad range of stringency conditions, wherein the substantially identical amino acid sequences include mutant sequences which vary by one or more substitutions, deletions or additions wherein at least some undefined biological activity of the protein is retained (see pages 8-9 of the specification), does not enable the claimed invention.

It is noted that neither the claims nor the specification limit TIE-2 polypeptide to a polypeptide that has the ability to inhibit angiogenesis or to prevent metastasis or invasive tumor growth. Further, the invention is based on cell line-derived information and for the reasons of record, it cannot be predicted that the invention would function as claimed, (b')(c') although the specification enables a method of detecting tamoxifen-resistant MCF-7 breast cancer cells comprising assay for the overexpression of a high molecular weight, 220 kDA putative TIE-2 related polypeptide, for the reasons of record, cell-lined derived information does not enable the broadly claimed invention. It is noted that Applicant does not address the teachings of Dermer, Drexler et al, Zellner et al, Embleton et al, Hsu et al.

Applicant argues that (d) the examples in the specification are drawn to *in vivo* conditions and not *in vitro* conditions, that is MCF-7 tumors grown in mice wherein after initial growth suppression, the tumors became resistant and growth resumed and Examiner has not met the burden to demonstrate that tumors that develop as a result of cell line inoculation into animals have different characteristics than primary tumors since the Action does not present any studies demonstrating any such differences, (e) the Action appears to be arguing that the examples disclosed in Applicants' specification are insufficient to support the claims because the examples do not disclose each and every condition under which tamoxifen-resistant breast cancer develops, however the existing examples are more than sufficient to support enablement of the claimed inveniton since those of skill in art understand conditions under which tamoxifen-resistant breast cancer develops, (f) compliance with the enablement requirement does not turn on whether an example is disclosed and an example is not needed if the invention is

otherwise disclosed in such a manner that one skilled in the art would be able to practice it without undue experimentation.

The arguments have been considered but have not been found persuasive because (d') given the known artifactural nature of cell lines, given the teachings of Dermer, Drexler et al, Zellner et al, Embleton et al, Hsu et al, no one of ordinary skill in the art would believe it more likely than not that the invention would function as claimed based only on the MCF-7-cell line derived information. Although this type of information is considered convincing, for example where a protein is known to be expressed by both *in vivo* tumor and cell-line-derived tumor wherein a specific treatment directed to that protein is shown to be effective in an animal model, it is not considered convincing in the instant case wherein the specification specifically states that "the present invention is the first to report an association between the development of tamoxifen resistance and the differential expression of ..... factors" which clearly refers to TIE-2 overexpression, wherein there is no demonstration of differential expression of TIE-2 in either primary or metastatic tamoxifen-resistant breast cancer samples compared to normal controls and compared to tamoxifen-responsive breast cancer samples, (e') contrary to Applicant's arguments, Examiner does not argue that the specification is not enabling because the examples do not disclose each and every condition under which tamoxifen-resistant breast cancer develops, rather Examiner has clearly stated that, given the known artifactural nature of cell-lines, given the known differences between cultured cells and primary or metastatic cancer cells, in the absence of data from primary sources, it cannot be predicted that the finding of over-expression of TIE-2 in a tamoxifen resistant breast cancer cell line-derived tumor would also be found in primary or metastatic breast cancer cells, (f')

although compliance with the enablement requirement does not turn on whether an example is disclosed and an example is not needed if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it without undue experimentation, in the instant case for the reasons of record, the invention is not disclosed in such a manner that one skilled in the art would be able to practice it without undue experimentation. Further, Applicant clearly recites the factors to be considered in determining whether there is sufficient evidence to meet the enablement requirement on page 10 of the Response. In reviewing Applicant's disclose of the factors the previous Action specifically showed why the claims were overly broad, specifically showed that the invention was the first of its kind, specifically showed that those of ordinary skill in the art understand that information based on cultured cell data is unpredictable, specifically showed that the working examples were not commensurate in scope with the claimed invention and why no nexus could be established between the working examples and the claimed invention. Examiner's analysis included all of the evidence related to each of these factors and concluded, based on the evidence and what was known in the art at the time the invention was made that the specification as originally filed does not enable the claimed invention.

Applicant argues that (g) the difference in TIE-2 protein in HuVec cells, 140 kDa, and the 220 kDa high molecular weight form of a putative TIE-2 related protein found in the tamoxifen-resistant tumor is not the result of a cell line-related artifact, rather than a change associated with tamoxifen-resistant breast cancer and reiterates arguments that the Action has failed to set forth any evidence that tumors grown in animals following inoculation of a cell culture line demonstrate characteristics that differ from the primary tumor, (h) the allegation set forth in the

action that the difference between the expression of the two different TIE-2 proteins is an artifact is mere speculation on the part of the Examiner, (i) the Action has failed to meet the burden of proof demonstrating differences in TIE-2 between tissue grown *in vitro* and tissue grown *in vivo*.

The arguments have been considered but have not been found persuasive because (g') the argument has not been found persuasive for the reasons set forth above, (h') the artifactural nature of cell lines is not mere speculation on the part of the Examiner, it is suggested that Applicant review Dermer, Drexler et al, Zellner et al, Embleton et al, Hsu et al, all of record, (I') again, the MCF-7-derived mouse tumors are tumors that are derived from cultured cells wherein cultured cells are known to be different than primary tumor cells, given this fact, no one of ordinary skill would believe it more likely than not that the invention would function as claimed based only on the information in the specification and known in the art.

Applicant argues that (j) the "abounding evidence" fails to support the notion that overexpression of TIE-2 mRNA gene product does not correlate with TIE-2 protein expression since none of the studies cited in the Action pertain to breast cancer or the TIE-2 protein and it is well known in the art that increases in mRNA levels are often associated with a parallel increase in expression of the associated protein and the presence of a few exceptions in the vast field of oncology does not support lack of enablement for the claimed invention, (k) the determination of enablement is based on the evidence as a whole.

The arguments have been considered but have not been found persuasive because (j') contrary to Applicant's arguments, Examiner does not state that TIE-2 mRNA gene product overexpression does not correlate with TIE-2 protein expression, but rather, Examiner states that it was conventionally understood at the

time the invention was made that protein overexpression could not be predicted based only on mRNA overexpression. Further, although the cited references are not drawn to TIE-2 or breast cancer, they clearly demonstrate the state of the art and that it was conventionally understood at the time the invention was made that the level of a specific mRNA expressed by a cancer cell is not predictably paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational modification. Applicant is clearly aware of this unpredictability in his statement that "increases in mRNA levels are often associated with a parallel increase in expression of the associated protein". Applicant is clearly aware that in the absence of objective evidence it is not possible to determine whether said parallel is fact found in the tamoxifen-resistant primary or metastatic cells, (k') based on the evidence as a whole, the claimed invention is not enabled for the reasons of record.

Applicant argues that (l) Tockman does not address biomarkers for breast cancer and whether or not Tockman et al should be applied to biomarkers for cancers other than lung cancer is inapplicable to the issue at hand. The issue is whether Applicants' specification as written contains information that is sufficient to enable the claimed invention. Applicant reiterates arguments drawn to the examples, (m) the Action appears to require that human data be provided in the Examples since use of the claimed invention for determination of tamoxifen-resistant breast cancer in humans is contemplated, however this is not the case since the specification need not contain an example if the invention is otherwise disclosed in such a manner that one skill in the art will be able to practice it without undue experimentation, (n) the MPEP states that representative examples will ordinarily be sufficient to enable the claimed invention.

The arguments have been considered but has not been found persuasive because (l') Applicants' specification as written does not contain information that is sufficient to enable the claimed invention for the reasons set forth previously and above. Further, although Tockman et al does not address biomarkers for breast cancer, the reference clearly established conditions necessary in bringing a cancer marker to successful clinical application and thus is clearly relevant to the instant rejection. In the absence of objective evidence demonstrating overexpression of TIE-2 polypeptide in primary tamoxifen-resistant breast cancer cells, compared to both normal breast and primary tamoxifen-sensitive breast cancer cells, it cannot be predicted that the claimed invention can function as claimed for the reasons set forth above. The arguments drawn to the examples are not persuasive for the reasons set forth above, (m') contrary to Applicant's arguments, Examiner does not require human data because the invention is clearly enabled for detecting tamoxifen-resistant MCF-7 breast cancer cells comprising assaying for the overexpression of a high molecular weight, 220 kDa putative TIE-2 related polypeptide. However, in order to be enabled for the scope of the claims, and to be awarded patent protection for the instant method as contemplated in human breast cancer patients, due to the undeveloped nature of the invention, due to the known artifactural nature of cultured cells, in the absence of objective evidence, the broadly claimed invention is not enabled. It is noted that Applicant was previously informed, on page 11 of the previous action, that "presentation of objective data demonstrating that upregulated expression of 220 kDA putative TIE-2 related protein in primary human breast tumors detects/diagnoses/provides a prediction of the existence of tamoxifen-resistant breast cancer cells would obviate" the rejection. It is also noted that Applicant has chosen not to submit said evidence.

Applicant argues that the Action admits that claims 22-25 are enabled given Examiner's statement that the specification is enabling for a method of detecting tamoxifen-resistant MCF-7 cells comprising assaying for the overexpression of a high molecular weight 220 kDa putative TIE-2 related polypeptide. The argument has been considered but has not been found persuasive because none of the newly added claims contains the combination of enabling parameters. That is none of the newly added claims include both MCF-7and a molecular weight of 220 kDa.

The arguments have been carefully considered but have not been found persuasive and the rejection is maintained.

5. All other rejections and objections recited in the paper mailed October 14, 2003 are hereby withdrawn.

6. No claims allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0837. The fax phone number for this Art Unit is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
July 8, 2004